PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 5199-17 PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/20399	International filing date *(day/month/year)* 26 June 2003 (26.06.2003)	Priority date *(day/month/year)* 16 July 2002 (16.07.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): C12N 15/85, 15/86; A61K 38/00, 39/395; C12Q 1/70; G01N 33/53 and US Cl.: 514/1,2; 424/130.1; 435/4, 7.1, 7.21, 325		
Applicant THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report
   II ☐ Priority
   III ☒ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   IV ☒ Lack of unity of invention
   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12 February 2004 (12.02.2004)	04 April 2005 (04.04.2005)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/ US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Christopher J. Nichols, Ph.D. J. Roberts for Telephone No. (571) 272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

Applicants: Thomas M. Jessell, et al.
Serial Number: 10/789,308
Filing Date: February 26, 2004
Exhibit 54

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/20399

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description:
pages 1-52 as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the claims:
pages 53-64 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the drawings:
pages 1-10 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 27,28 and 55-102

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 27,28 and 55-102

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

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IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention is accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

According to PCT Rule 13.2, unity of invention exists only when the shared same or corresponding technical feature is a contribution over the prior art. The inventions listed as Groups 1 and 6 do not relate to a single general inventive concept because they lack the same or corresponding special technical feature.

Group 1, claim(s) 1-26 and 29-54, drawn to a method of inducing differentiation of an embryonic stem cell comprising contacting said cell with amounts of a rostralizing and/or caudalizing embryonic signaling factor and a dorsalizing or ventralizing embryonic signaling factor and transplanting said cells.

Group 1 is drawn to the special technical feature of inducing differentiation of an embroyonic stem cell, which is not shared by any of the other groups.

Group 6, claim(s) 103-105, drawn to a method for identifying an agent.

The technical feature of Group 1 is a method of inducing differentiation of an embryonic stem cell comprising contacting said cell with amounts of a rostralizing and/or caudalizing embryonic signaling factor such as FGF and a dorsalizing or ventralizing embryonic signaling factor such as BMP which is shown by US 5,851,832 (Weiss et al.) 22 December 1998 to lack novelty or inventive step and does not make it a contribution over the prior art. US 5,851,832 teaches the incubation of neurospheres, a small cluster of embryonic stem cells with bFGF, a type of FGF, and BMP-2, a type of BMP (Table II).

Group 6 is drawn to the special technical feature of a method for identifying an agent, which is not shared by any of the other groups.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-26,29-54 and 103-105

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V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO
Inventive Step (IS)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO
Industrial Applicability (IA)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO

2. CITATIONS AND EXPLANATIONS
Please See Continuation Sheet

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

V.1. Reasoned Statements:
The opinion as to Novelty was positive (Yes)with respect to claims 4, 5, 7-11, 13-25, 29, 32-33, 35-38, 40-54, 104-105
The opinion as to Novelty was negative (No) with respect to claims 1, 2, 3, 6, 12, 26, 30, 31, 34, 39, 103
The opinion as to Inventive Step was positive (Yes)with respect to claims 4, 5, 7-11, 13-25, 29, 32-33, 35-38, 40-54, 104-105
The opinion as to Inventive Step was negative(NO) with respect to claims 1, 2, 3, 6, 12, 26, 30, 31, 34, 39, 103
The opinion as to Industrial Applicability was positive (YES) with respect to claims 1-26, 29-54, 103-105
The opinion as to Industrial Applicability was negative(NO) with respect to claims NONE

Claims 1, 2, 3, 6, 12, 26, 30, 31, 34, 39, and 103 lack novelty under PCT Article 33(2) as being anticipated by US 5,581,832 A (WEISS et al.) 22 December 1998 (22.12.1998). US 5,581,832 teaches a method for inducing differentiation of an embryonic stem cell into a differentiated neural cell and a method of screening for agents comprising same thus meeting the limitations of claims 1, 26, and 103 (Col. 11; Table II). US 5,581,832 teaches that said embryonic stem cells differentiate into astrocytes, neurons, and oligodendrocytes thus meeting the limitations of claims 6, 12, 34, and 39 (Figures 1 & 3; Col. 10). US 5,581,832 teaches the following rostralizing and/or caudalizing embryonic signaling factors- FGF (Col. 16). US 5,581,832 teaches the following dorsalizing or ventralizing embryonic signaling factors- BMP (Col. 31). US 5,581,832 teaches the above methods wherein said cells may be mouse or human thus meeting the limitations of claims 2, 3, 30, and 31 (Col. 13).

Claims 1, 2, 3, 6, 12, 26, 30, 31, 34, 39, and 103 lack novelty under PCT Article 33(2) as being anticipated by US 6,294,346 B1 (WEISS et al.) 25 September 2001 (25.09.2001). US 6,294,346 teaches a method for inducing differentiation of an embryonic stem cell into a differentiated neural cell and a method of screening for agents comprising same thus meeting the limitations of claims 1, 26, and 103 (Table II; Examples 8-9). US 6,294,346 teaches that said embryonic stem cells differentiate into astrocytes, neurons, and oligodendrocytes thus meeting the limitations of claims 6, 12, 34, and 39 (Figures 1 & 3; Col. 10). US 6,294,346 teaches the following rostralizing and/or caudalizing embryonic signaling factors- FGF (Col. 16). US 6,294,346 teaches the following dorsalizing or ventralizing embryonic signaling factors- BMP (Col. 31). US 6,294,346 teaches the above methods wherein said cells may be mouse or human thus meeting the limitations of claims 2, 3, 30, and 31 (Col. 13).

Claims 1, 2, 3, 6, 12, 26, 30, 31, 34, 39, and 103 lack novelty under PCT Article 33(2) as being anticipated by US 5,980,885 A (WEISS et al.) 09 November 1999 (09.11.1999). US 5,980,885 teaches a method for inducing differentiation of an embryonic stem cell into a differentiated neural cell and a method of screening for agents comprising same thus meeting the limitations of claims 1, 26, and 103 (Table II; Examples 8-9). US 5,980,885 teaches that said embryonic stem cells differentiate into astrocytes, neurons, and oligodendrocytes thus meeting the limitations of claims 6, 12, 34, and 39 (Figures 1 & 3; Col. 10). US 5,980,885 teaches the following rostralizing and/or caudalizing embryonic signaling factors- FGF (Col. 16). US 5,980,885 teaches the following dorsalizing or ventralizing embryonic signaling factors- BMP (Col. 31). US 5,980,885 teaches the above methods wherein said cells may be mouse or human thus meeting the limitations of claims 2, 3, 30, and 31 (Col. 13).

Claims 1, 2, 3, 6, 12, 26, 30, 31, 34, 39, and 103 lack an inventive step under PCT Article 33(3) as being obvious over US 5,581,832 A (WEISS et al.) 22 December 1998 (22.12.1998). Claims lacking in novelty also lack an inventive step.

Claims 1, 2, 3, 6, 12, 26, 30, 31, 34, 39, and 103 lack an inventive step under PCT Article 33(3) as being obvious over US 6,294,346 B1 (WEISS et al.) 25 September 2001 (25.09.2001). Claims lacking in novelty also lack an inventive step.

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Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Claims 1, 2, 3, 6, 12, 26, 30, 31, 34, 39, and 103 lack an inventive step under PCT Article 33(3) as being obvious over US 5,980,885 A (WEISS et al.) 09 November 1999 (09.11.1999). Claims lacking in novelty also lack an inventive step.

Claims 4, 5, 7-11, 13-25, 29, 32-33, 35-38, 40-54, and 104-105 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the aspects of the inventions claimed therein.

Claims 1-26, 29-54, and 103-105 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.